Recombinant tissue plasminogen activator (rtPA) is licensed for treatment of selected patients within 3 hours of acute ischemic stroke in many parts of the world. Its clinical use is highly variable. This is an update of the 1999 version of the Cochrane review.

Objectives
The aim of this study was to assess the effect of thrombolysis given within 6 hours of acute ischemic stroke, whether particular categories of patients are more likely to benefit, and where more data are needed from randomized trials.

Search Strategy
We searched the Cochrane Stroke Group Trials Register (to January 2003), MEDLINE (1966 through January 2003), and EMBASE (1980 through January 2003). We also contacted researchers and pharmaceutical companies, attended relevant conferences, and hand-searched 4 Japanese journals.

Selection Criteria and Data Collection and Analysis
Selected were unconfounded randomized controlled trials comparing any thrombolytic agent with control in patients with definite acute ischemic stroke, which measured functional outcome (death or dependency; modified Rankin 3 to 6) at more than 1 month after stroke. Data were extracted and verified with principal investigators of all major trials. Published and unpublished data were used.

Main Results
Eighteen trials comprising 5727 patients were included in trials testing urokinase (UK), streptokinase, recombinant pro-UK, or rtPA. Trials testing rtPA contributed ~50% of the data (patients and trials); 1 new trial of UK in 565 patients was identified; 4984 patients (15 trials) were treated within 6 hours of stroke; and 16 trials used intravenous administration (96% of patients; Figure).

Overall, among patients treated up to 6 hours after ischemic stroke, despite an increase in intracranial hemorrhage (fetal intracranial hemorrhage odds ratio [OR], 4.34; 95% CI, 3.14, 5.99 and symptomatic intracranial hemorrhage OR, 3.37; 95% CI, 2.68, 4.22) and death by 3 to 6 months (OR, 1.33; 95% CI, 1.15, 1.53), thrombolysis reduced the proportion of patients with poor functional outcome at 3 to 6 month follow-up (OR 0.84; 95% CI, 0.75, 0.95). There was heterogeneity of treatment effect for poor functional outcome and deaths at the end of follow-up but not for intracranial hemorrhage. We undertook subgroup analyses to explore potential sources of heterogeneity including (1) thrombolytic drug, (2) time to treatment, (3) concomitant aspirin and heparin use, (4) the patients’ age, and (5) the severity of the stroke.

1. Trials of intravenous rtPA given up to 6 hours after stroke suggested that it could be associated with more favorable risk/benefit ratio: poor functional outcome (OR, 0.80; 95% CI, 0.69, 0.93) and no significant excess of deaths at the end of follow-up (OR, 1.17; 95% CI, 0.95, 1.45). However, there are no direct randomized comparisons of rtPA with other thrombolytic drugs.

2. For treatment up to 3 hours after stroke (1311 patients, 50% of whom came from the National Institute of Neurological Disorders and Stroke [NINDS] Trial), thrombolytic therapy appeared more effective in reducing poor functional outcomes (all agents OR, 0.66; 95% CI, 0.53, 0.83; rtPA OR, 0.64; 95% CI, 0.5, 0.83) with no significant adverse effect on death at the end of follow-up (all agents OR, 1.13; 95% CI, 0.86, 1.48; rtPA OR, 0.97; 95% CI, 0.69, 1.36) but still an excess of symptomatic intracranial hemorrhage (rtPA OR, 3.40; 95% CI 1.48 to 7.84). However, comparing <3- with 3- to 6-hour treatment in rtPA trials, which randomized in both time windows, showed the same risk of death (<3 hours OR, 1.75; 95% CI, 0.91, 3.36; 3 to 6 hours OR, 1.38; 95% CI, 1.05, 1.82) and a nonsignificant trend for <3-hour treatment being better in terms of poor functional outcome (<3 hours OR, 0.69; 95% CI, 0.44, 1.09; 3 to 6 hours OR, 0.88; 95% CI, 0.73, 1.06). This suggests that some other time-related factor, like stroke severity, may also be important and requires further exploration in new trials to clarify the relationship between “tissue injury” (ie, time and stroke severity) and rtPA.

3. Based mostly on nonrandom comparisons, antithrombotic drugs (aspirin or heparin) given soon after thrombolysis may increase the risk of death (all patients given antithrombotic drugs within 24 hours of thrombolysis, OR,
1.95; 95% CI, 1.45, 2.62; no patients given antithrombotic drugs within 14 days, OR, 0.89; 95% CI, 0.58, 1.37). Tabular data were not available in sufficient detail to assess the effect of aspirin use before the stroke.

4. There were too few data from patients aged >80 years (42 in total from all trials of rtPA combined) to assess the effect of thrombolysis in older patients.

5. Tabular data were not available in sufficient detail to assess the effect of stroke severity.

**Reviewers’ Conclusions**

Overall, thrombolytic therapy given within 6 hours of stroke reduced death or dependency (ie, more patients alive and independent) at 3 to 6 months. This appears to be despite an increase in early and late deaths, mostly from intracranial hemorrhage. The benefits seem to be greater with thrombolysis given sooner after stroke. rtPA may be associated with less hazard and more benefit. The data justify the use of thrombolytic therapy with intravenous rtPA in highly selected patients where a license exists. However, the optimum criteria to identify the patients most likely to benefit and least likely to be harmed, the latest time window, and the effect of prior aspirin use, increasing patient age, stroke severity, agent, dose, and route of administration are not clear. Further randomized controlled trials are therefore needed.


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**Key Words**: brain ischemia ■ thrombolysis ■ tissue plasminogen activator ■ stroke, acute